SUMMARY OF SAFETY AND EFFECTIVENESS

1. General Information

1.1. Name and Address of Applicant

Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, IN 46256 USA
Establishment 1823260

1.2. Device Trade Name(s):

Elecsys® HBsAg Immunoassay
Elecsys® HBsAg Confirmatory Test
Elecsys® PreciControl HBsAg

1.3. Device Generic Names:

Hepatitis B Surface Antigen (HBsAg) Assay
Hepatitis B Surface Antigen (HBsAg) Control
Hepatitis B Surface Antigen (HBsAg) Confirmatory Kit

1.4. PMA Number:

P990012

1.5. Date of Panel Recommendation:

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

1.6. Date of Notice of Approval to Applicant:

June 1, 2001

2. Indications for Use

2.1. Elecsys® HBsAg Immunoassay

For the in vitro test qualitative detection of hepatitis B surface antigen (HBsAg) in human serum or plasma (sodium heparin, EDTA-K3 and sodium citrate).

Assay results, in conjunction with other serological and clinical information may be used for the laboratory diagnosis of individuals with acute or chronic hepatitis B. This assay may be used to screen for hepatitis B infection in pregnant women to identify neonates who are at high risk of acquiring HBV during the perinatal period.

This assay is intended only for use on the Elecsys® 2010 immunoassay analyzer, and is based on electrochemiluminescence immunoassay technology ("ECLIA").

2.2. Elecsys® PreciControl HBsAg

For the quality control of the Elecsys HBsAg Immunoassay and Elecsys HBsAg Confirmatory Test when testing human serum. The performance of the PreciControl HBsAg has not been established with any other HBsAg assay.

PreciControl HBsAg is not a calibrator and should not be used for assay calibration.

2.3. Elecsys® HBsAg Confirmatory Assay

For the in vitro qualitative confirmation of the presence of hepatitis B surface antigen in human serum or plasma (sodium heparin, EDTA-K3 and sodium citrate) found repeatedly reactive by the Elecsys HBsAg Immunoassay.

This assay is intended only for use on the Elecsys® 2010 immunoassay analyzer. The performance of the Elecsys HBsAg Confirmatory Test has not been established with any other HBsAg immunoassay.

3. Device Description

3.1. Principle of Device Methodology

3.1.1. The Elecsys® HBsAg Immunoassay:

Is used for the measurement of hepatitis B surface antigen (HBsAg) in human serum and plasma (sodium heparin, EDTA-K3, sodium citrate). The assay is based on the principles of electrochemiluminescence.

In the first incubation, HBsAg in the sample, a biotinylated monoclonal HBsAg-specific antibody and a monoclonal HBsAg-specific antibody labeled with a ruthenium complex react to form a "sandwich" complex. After the addition of streptavidin-coated microparticles the complex becomes bound to the solid phase via interaction of biotin and streptavidin. After incubation the reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with a buffer. Application of a voltage to the electrode then induces chemiluminescent emission that is measured by a photomultiplier. Results are determined automatically by the Elecsys software by comparing the

electrochemiluminescence signal obtained from the sample with the cutoff value previously obtained by HBsAg calibration. The total duration of the assay is 18 minutes.

3.1.2. The Elecsys HBsAg Confirmatory Test:

Uses the principle of specific antibody neutralization to confirm the presence of HBsAg. Samples found to be repeatedly reactive in the Elecsys HBsAg Immunoassay test are treated in parallel with the confirmatory reagent (containing anti-HBs) and control reagent. During incubation the excess anti-HBs antibodies in the confirmatory reagent neutralize any HBsAg in the sample. In the subsequent Elecsys HBsAg immunoassay test this leads to a reduction in the cutoff index (COI) value (signal of sample/COI) in comparison to the value originally obtained for the sample.

3.1.3. The Elecsys PreciControl HBsAg:

Contains human serum in the negative and positive concentration range that are used for monitoring the accuracy of Elecsys HBsAg immunoassay.

3.2. Kit Configuration and Component

3.2.1. The Elecsys® HBsAg Immunoassay is composed of five reagents:

- The M reagent consists of Streptavidin coated microparticles ("beads") in HEPES (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid) buffer with preservative.
- The R1 reagent, Anti-HBsAg-Ab-biotin, consists of purified, biotinylated anti-HBsAg antibody (mouse monoclonal directed against the "a" region determinant) in a phosphate buffer solution with preservative.
- The R2 reagent, Anti-HBsAg-Ab~$Ru(bpy)_3^{2+}$, consists of purified anti-HBsAg antibodies (mouse monoclonal directed against the "a" region determinant) labeled with ruthenium complex in a phosphate buffer solution with preservative.
- Cal 1, Negative Calibrator for five calibrations, consists of human serum, non-reactive for HBsAg, anti-HBs, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.
- Cal 2, Positive Calibrator for five calibrations, consists of HBsAg 0.5 IU/mL (subtype *ad*) in human serum, non-reactive for anti-HBs, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.

3.2.2. The Elecsys PreciControl HBsAg contains two reagents

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- PreciControl 1, PC HBsAg 1, consists of human serum, non-reactive for HBsAg, anti-HBs, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.

- PreciControl 2, PC HBsAg 2, consists of HBsAg (human, unspecified "a" subtype) at approximately 0.2 IU/mL in human serum, non-reactive for anti-HBs, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.

3.2.3. The Elecsys HBsAg Confirmatory Test contains two reagents

- The confirmatory reagent, bottle 1, consists of anti-HBs (human) ≥ 200,000 IU/mL in human serum, non-reactive for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.

- The control reagent, bottle 2, consists of human serum, non-reactive for HBsAg, anti-HBs, anti-HCV, anti-HIV-1 and anti-HIV-2 with preservative.

4. Contraindications

There are no known contraindications for the Elecsys® HBsAg Immunoassay.

5. Warnings and Precautions

For *in vitro* diagnostic used only.

Warnings and precautions are stated in the attached product labeling.

6. Alternative Practices and Procedures

There are currently several FDA approved and licensed in vitro diagnostic tests for serological markers of hepatitis B virus (HBV) infection when used in conjunction with a patient's medical history, clinical examination, and other findings can be used for diagnostic purposes.

7. Prior Marketing History

The Elecsys® HBsAg Immunoassay, Elecsys HBsAg Confirmatory Test, and Elecsys PreciControl HBsAg has been marketed worldwide since 1998. The following list represents the countries where these devices have been marketed.

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Argentina	Asia Pacific	Athens	Australia	Austria	Bahrain
Belarus	Belgium	Bosnia & Herzegovina	Brazil	Brazil	Budapest
Bulgaria	Canada	Cyprus	Egypt	Estonia	France
Germany	Hong Kong	Hungary	Iceland	Israel	Italy
Japan	Johannesburg	Jordan	Korea	Lebanon	Libyan Arab Jamahiriya
Lima	Lithuania	Luxembourg	Malta	Marokko	Mexico
Montevideo	Morocco	Moscow	Netherlands	New Zealand	Nigeria
Oman	Polska	Prague	Quito	Romania	Saudi Arabia
Slovenia	Spain	Spain	Switzerland	Syrian Arab Republic	Thailand
Tunisia	Turkey	UK	United Arab Emirates	Uruguay	Venezuela

The device has not been withdrawn from marketing in any country for reasons relating to the safety and effectiveness of the device.

8. Potential Adverse Effects of the Device on Health

As an *in vitro* diagnostic, there is no direct adverse effect of the Elecsys HBsAg immunoassay test system on the health of the patient.

The possibility of erroneous test results due to test malfunctions or operator errors exists. An erroneously elevated test result could theoretically result in unnecessary treatment, however, as the Elecsys HBsAg Confirmatory Test is required for all repeatedly reactive test results, the likelihood of a false positive is low.

An erroneously nonreactive test result may lead to misdiagnosis, lack of treatment and a possible worsening of the patient's condition, as well as potential for the spread of infection from the patient to uninfected persons.

It is recognized that presently available methods for the detection of hepatitis B surface antigen may not detect all potentially infected individuals. A nonreactive test result does not exclude the possibility of exposure to or infection with hepatitis B. Non-reactive results in individuals with prior exposure to hepatitis B may be due to antigen levels being below the detection limits of this assay or lack of antigen reactivity to the antibodies used in this assay. A falsely negative result for samples containing HBV mutants cannot be ruled out using the Elecsys HBsAg immunoassay. Testing using alternative methodologies may be warranted if signs, symptoms, and risk factors are indicative of viral hepatitis.

A false, transient positive result may occur in individuals recently vaccinated for hepatitis B because of its presence in the vaccine.

As with all tests containing monoclonal mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes. In rare cases, interference due to extremely high titers of antibodies to streptavidin and ruthenium can occur.

The risk of incorrect test results is inherent with all in vitro diagnostic products. Therefore, the above potential risks are not unusual in the laboratory setting. Appropriate warnings for each of these risks are contained in the labeling and package insert instructions. Standard good laboratory practices are considered sufficient to minimize risks to the end user.

9. Summary of Non-Clinical Studies

All studies were performed using the Elecsys 2010 Immunoassay Analyzer.

9.1. Analytical Sensitivity

The Elecsys HBsAg Immunoassay calibrators are standardized against the WHO 1st International Standard (subtype ad, Code 80/549, 1985). Paul Erlich Institute (PEI) standards were also measured by the Elecsys HBsAg Immunoassay and compared with the WHO standard.

The PEI reference material 1A (1992) showed the closest fit to the WHO reference material (1 E/ml PEI (1A) = 1.23 IU/ml WHO). Two analytical sensitivity studies were conducted during the non-clinical PMA studies to assess the sensitivity based upon the above assay standardization.

In the first study serial dilutions of reference standard materials were tested. The limit of detection was interpolated as the HBsAg concentration at which the test signal equaled the cutoff value (COI=1.0). Using the WHO 1st International Standard (subtype *ad*, 1985), the Elecsys HBsAg Immunoassay limit of detection (LOD) was 0.028 IU/mL (95% CI = 0.024 – 0.032 IU/mL). Similar results were obtained with the PEI standard (PEI reference material No.1, subtype *ad*), where the Elecsys limit of detection was 0.010 E/mL (95% CI = 0.009 – 0.011 E/mL).

9.2. Seroconversion Panels

A total of nine seroconversion panels from commercial vendors were tested at one of the clinical sites by the Elecsys HBsAg immunoassay and the reference HBsAg assay. The following table presents a summary of the Elecsys HBsAg immunoassay test system results for the nine panels in comparison to the reference method. Elecsys results were comparable to the FDA-licensed reference test.

Panel ID	Days to HBsAg Reactive Result (Reference HBsAg Assay)	Days to HBsAg Reactive Result (Elecsys HBsAg Assay)	Difference in Days to HBsAg Reactive Result (Reference – Elecsys)
01005	16	16	0
11004	26	26	0
40565L	5	5	0
51005	0	0	0
21469D	0	0	0
22663D	17	17 *	0
PHM902	71	71	0
PHM907	50	50	0
PHM919	19	19 **	0
PHM920	26	26	0

* Initial reactive results only, quantity not sufficient to perform confirmatory with either assay.

** Sample was reactive on Day 14 by Elecsys only, but without confirmation.

9.3. Antibody Specificity

A search of the "BLAST" database (http://www.ncbi.nlm.nih.gov/blast) for protein sequence homology to other than HBV was performed for the two mouse monoclonal antibodies (Mabs) used in the Elecsys 2010 HBsAg immunoassay. The biotinylated Mab was found to be highly specific to a conformational epitope of HBsAg "a" region determinant while the ruthenylated-Mab showed no relevant sequence homology with any known virus other than its designated target. The results of the search are interpreted as evidence that cross-reactivity by the kit Mabs to other non-HBV viruses is highly remote.

9.4. Matrix Effects:

Studies were conducted to verify the types of blood collection tubes that can be used with the Elecsys HBsAg Immunoassay. EDTA–K_3 plasma, sodium heparin plasma, sodium citrate plasma, and serum containing gel separator (serum separator tube, SST) were evaluated compared to serum. The format was to test 10 unspiked and 10 spiked with varying levels of HBsAg. The results of these studies demonstrated that serum collected using standard sampling tubes or tubes containing separating gel (SST's) may be used in these assays. In addition plasma collected with sodium heparin, EDTA-K_3, or sodium citrate may also be used.

9.5. Endogenous Interference

Samples with abnormally elevated levels of hemoglobin, lipids, bilirubin, total protein, heparin, and biotin were simulated using patient samples (negative and HBsAg positive) spiked with the endogenous analyte of interest and compared to controls. The concentrations evaluated are summarized in the following table.

Endogenous Substance	Concentration Evaluated	Solvent	Reference Range
Hemoglobin	1600 mg/dl	Serum	0.5 - 5.0 mg/dl
Lipids	1500 mg/dl	distilled/deionized water	10 - 190 mg/dl
Bilirubin	30 mg/dl	0.1 N NaOH	0.1 to 1.2 mg/dl
Total Protein	12 g/dl	Serum	6.0 - 7.8 g/dl
Heparin	10 U/ml	Serum	0.05 - 1.0 U/ml
Biotin	50 ng/ml	10 mM K_2PO_4	0.06 - 0.43 ng/ml

The results of this study demonstrated that samples containing hemoglobin concentrations up to 1600 mg/dl, triglyceride levels up to 1500 mg/dl, bilirubin levels up to 30 mg/dl, total protein levels up to 12 g/dl, heparin levels up to 10 U/ml, or biotin levels up to 50 ng/ml may be tested accurately with the Elecsys HBsAg Immunoassay.

9.6. Carryover Study

A study using the Elecsys HBsAg Immunoassay was done to evaluate the effect of a sample highly reactive for HBsAg on a following negative sample. Two patient samples highly reactive for HBsAg were evaluated in this study. Sample 1, highly reactive for HBsAg (approximately 3000 COI) was tested in three sample cups (H1, H2, H3) followed by replicates of an HBsAg negative pool tested in five sample cups (L1, L2, L3, L4, L5). This sequence was repeated nine times in the same run for a total of ten high-low series. The study was repeated using a second HBsAg positive sample (Sample 2) with a COI of approximately 1900. The same testing sequence was performed as described for Sample 1. The results from this study showed that clinically significant carryover was not observed on the Elecsys HBsAg Immunoassay when testing highly positive HBsAg samples.

9.7. High Dose Hook Effect

Studies were run to assess the potential for a high dose hook effect (prozone effect). Samples with highly elevated levels of HBsAg were diluted with HBsAg negative serum. The diluted and undiluted samples were tested by the Elecsys HBsAg Immunoassay. A hook effect was observed for the Elecsys HBsAg Immunoassay, however samples with HBsAg concentrations up to 2,000,000 IU/mL were detected as reactive by the Elecsys HBsAg Immunoassay and did not produce false negative test results.

9.8. Establishment of Cutoff

The cutoff for the Elecsys 2010 HBsAg immunoassay was established by testing a 175-member panel of well characterized HBsAg specimens with three kit lots followed by testing on two kits lots with over 2,800 specimens including subjects at various risk for HBV infection, sensitivity, specificity and seroconversion panels and dilution series of both international reference materials and HBsAg positive samples. Using these data, the cutoff value that allowed for optimal discrimination between negative and positive specimens was determined.

9.9. Stability Studies

To assess the real-time stability, whole kit samples were randomly selected from the individual lots of finished product. The kits and reagents were stored at the recommended storage temperature of 2-8°C, in temperature-controlled cabinets, for the duration of the ongoing stability studies. Temperatures in the storage cabinets were checked at regular intervals. The test measurement intervals started with the production date of the last kit reagent in the released kits, and continued at approximate 1, 3, 6, 9, 12, 15, 18, 24, and 30 month time intervals. Key stability parameters monitored for the Elecsys HBsAg Immunoassay were analytical sensitivity, results of internal control samples and the assay "Test Dynamic" (defined as quotient of the COI of Cal 2 over the COI of Cal 1).

Based upon the results of real-time stability studies, the current shelf life for the Elecsys HBsAg Immunoassay is eleven (11) months, nine (9) months for the Elecsys HBsAg Confirmatory Test, and twelve (12) months for the Elecsys HBsAg PreciControls when the reagents are stored at 2-8°C.

The stability of kit reagents after temperature stress conditions was examined in several studies using different stress models. The results from the temperature stress studies indicated stability for all Elecsys HBsAg Immunoassay, Confirmatory Test, and PreciControl reagents for at least 1 week at 35°C. The recommended storage temperature for all the reagents is 2-8°C.

Additional opened reagent and on-board stability studies were conducted which demonstrated the following:

- The Elecsys HBsAg Immunoassay and Elecsys HBsAg PreciControl kits may be used for 12 weeks once opened, when stored at 2-8°C,
- The Elecsys HBsAg Confirmatory Test may be used for 8 weeks once opened, when stored at 2-8°C,
- The Elecsys HBsAg Immunoassay reagent kit is stable on-board the Elecsys 2010 for 4 weeks,
- An Elecsys HBsAg Immunoassay calibrator set may be used for up to 5 calibration events and may stored on-board the Elecsys 2010 for up to 5 hours at 32°C.
- An Elecsys HBsAg PreciControl set can be used for up to 7 quality control procedures and may be stored on-board the Elecsys 2010 for up to seven hours at 32°C.

The results from the sample stability study demonstrated that serum samples containing HBsAg are stable for at least ten days when stored at 2–8°C. The results of a second ongoing long-term sample stability study found that serum samples are stable for at least six months when stored at -20°C. In a third sample stability study (sample freeze/thaw experiment), it was shown that samples may be frozen at least six times without affecting Elecsys HBsAg Immunoassay results.

Results from calibration stability studies found that a single Lot Calibration can be used for one month with multiple reagent packs, as long as the same reagent lot is used. A calibration on an individual reagent pack is stable for 7 days when using the same reagent kit stored on the analyzer.

9.10. Analytical Specificity

Patient samples with various disease states were evaluated to determine the analytical specificity of the Elecsys HBsAg Immunoassay. Comparisons were made between the Elecsys HBsAg Immunoassay final results and the determined HBV status using FDA licensed HBsAg testing. All three sites participated in this evaluation; however the analysis has been made with the data from all sites combined.

The table below summarizes the Elecsys HBsAg Immunoassay final test results compared to the HBV status for all sites combined.

Analytical Specificity Test Results: All Sites

Elecsys® HBsAg Immunoassay	**Neg**	**Neg**	**Pos**	**Pos**	**Total**
HBV Status	**Neg**	**Pos**	**Neg**	**Pos**	**Samples**
Other Viral Hepatitis Infections	46	0	0	0	46
Other Infectious Diseases	87	1	0	8	96
Non-Viral Liver Diseases	24	0	0	0	24
Autoimmune Diseases	19	0	0	1	20
High Risk Populations	30	0	0	1	31
Post Influenza Vaccination	5	0	0	0	5
Other Diseases	10	0	0	0	10
Total	221	1	0	10	232

The following sections present additional details to the table above by category.

Other Viral Hepatitis Infections: Elecsys Final Results

Elecsys HBsAg Immunoassay	**Neg**	**Neg**	**Pos**	**Pos**	**Total**
HBV Status	**Neg**	**Pos**	**Neg**	**Pos**	**Samples**
Hepatitis A Infection	4	0	0	0	4
Hepatitis C Infection	25	0	0	0	25
Hepatitis A/ Hepatitis C Co-infection	6	0	0	0	6
Hepatitis E Infection	11	0	0	0	11
Total	46	0	0	0	46

For patients with other viral hepatitis infections, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (46/46).

Other Infectious Diseases: Elecsys Final Results

Elecsys HBsAg Immunoassay	Neg	Neg	Pos	Pos	Total
HBV Status	Neg	Pos	Neg	Pos	Samples
Cytomegalovirus	10	0	0	0	10
Epstein-Barr Virus	10	0	0	0	10
Herpes Simplex Virus	13	1	0	0	14
Parvovirus B19	7	0	0	3	10
Rubella Virus	10	0	0	0	10
Human Immunodeficiency Virus	5	0	0	4	9
Syphilis	10	0	0	0	10
Toxoplasmosis	12	0	0	1	13
Escherichia coli	10	0	0	0	10
Total	87	1	0	8	96

One sample from a patient with Herpes Simplex Virus (HSV) was discrepant between the Elecsys HBsAg Immunoassay and the HBV status. The Elecsys HBsAg Immunoassay results for this sample were borderline negative. The sample was confirmed positive with the reference HBsAg assay. Of the other HBV serological tests, Anti-HBc was positive; HBV DNA test was also positive. Liver function testing was not performed. This patient was a male, age 38, race unknown, with concurrent HIV infection. No other clinical information was available; a subsequent sample was not available for testing.

As there were thirteen other samples positive for HSV that were nonreactive by the Elecsys HBsAg Immunoassay, there does not appear to be a generalized specificity issue of the Elecsys HBsAg Immunoassay with HSV positive samples. Furthermore, of the nine samples from patients positive for HIV, all Elecsys HBsAg Immunoassay results were in agreement with the HBV status, also indicating excellent specificity with HIV positive samples. It is unclear why this sample was not detected as positive by the Elecsys HBsAg Immunoassay. This sample is considered to be a false negative by the Elecsys HBsAg Immunoassay.

For patients with other infectious diseases, 99.0% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (95/96).

Non-Viral Liver Disease: Elecsys Final Results

Elecsys HBsAg Immunoassay	Neg	Neg	Pos	Pos	Total
HBV Status	Neg	Pos	Neg	Pos	Samples
Non-viral Liver Disease	20	0	0	0	20
Alcoholic Hepatitis	4	0	0	0	4
Total	24	0	0	0	24

For patients with non-viral liver diseases, including alcoholic hepatitis, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (24/24).

Autoimmune Diseases: Elecsys Final Results

Elecsys HBsAg Immunoassay	Neg	Neg	Pos	Pos	Total
HBV Status	Neg	Pos	Neg	Pos	Samples
Rheumatoid Factor	9	0	0	1	10
Antinuclear antibodies	10	0	0	0	10
Total	19	0	0	1	20

For patients with autoimmune diseases, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (20/20).

High Risk Populations: Elecsys Final Results

Elecsys HBsAg Immunoassay	**Neg**	**Neg**	**Pos**	**Pos**	**Total**
HBV Status	**Neg**	**Pos**	**Neg**	**Pos**	**Samples**
Transplant Recipients	11	0	0	0	11
Chronic Dialysis	10	0	0	0	10
Intravenous Drug Users	9	0	0	1	10
Total	30	0	0	1	31

For patients at high risk of acquiring HBV infection, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (31/31).

Post Influenza Vaccination: Elecsys Final Results

Elecsys HBsAg Immunoassay	**Neg**	**Neg**	**Pos**	**Pos**	**Total**
HBV Status	**Neg**	**Pos**	**Neg**	**Pos**	**Samples**
Post Influenza Vaccination	5	0	0	0	5

For patients having recently received a vaccination for influenza, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (5/5).

Other Diseases: Elecsys Final Results

Elecsys HBsAg Immunoassay	**Neg**	**Neg**	**Pos**	**Pos**	**Total**
HBV Status	**Neg**	**Pos**	**Neg**	**Pos**	**Samples**
Gammopathies	10	0	0	0	10

For patients with gammopathies, 100% agreement was observed between Elecsys HBsAg Immunoassay Final Results and the HBV status (10/10).

9.11. Reproducibility (Precision)

In a multi-center precision study with a design based on principles contained in the NCCLS draft guideline EP5-T2[1], results from a series of negative and positive samples run on the Elecsys 2010 analyzer at three centers over 20 days demonstrated a within run precision ranging from 1.3 to 7.5% CV. Between day precision, which also included within run and between run components, ranged from 4.6 to 16.3% CV; total precision, which included all precision components, ranged from 6.0 to 22.6% CV.

[1] National Committee for Clinical Laboratory Standards. Evaluation of Precision Performance of Clinical Chemistry Devices - Second Edition; Tentative Guideline. NCCLS document EP5-T2. NCCLS, 771 East Lancaster Avenue, Villanova, Pennsylvania 19085, 1992.

Reproducibility Study Results for the Elecsys HBsAg Immunoassay

Panel Member	Mean (COI)	Within Run		Between Day*		Total**	
		SD	CV	SD	CV	SD	CV
1	0.419	0.031	7.5%	0.069	16.3%	0.095	22.6%
2	0.767	0.052	6.7%	0.063	8.2%	0.105	13.7%
3	1.78	0.043	2.4%	0.109	6.1%	0.149	8.3%
4	19.13	0.254	1.3%	0.897	4.7%	1.139	6.0%
5	51.25	0.672	1.3%	2.435	4.7%	3.157	6.2%
6	100.9	1.276	1.3%	4.673	4.6%	6.031	6.0%

* Includes within run, between run and between day components.

** Includes within run, between run, between day, between site/ lot interaction, between lot and between site components.

Reproducibility of the manual test steps of the Elecsys HBsAg Confirmatory test was determined using three sera of differing HBsAg concentrations (8–10 times per sample with both the control and confirmatory reagents). After a 30-minute period of incubation at 20°C the pretreated samples were determined using Elecsys reagents, calibrators and controls. Representative data for manual sample pretreatment followed by assay on the Elecsys 2010 are shown below.

Intra-Assay Precision After Confirmatory Test Pretreatment

Sample	Confirmatory Sample			Control Sample		
	Mean (COI)	SD (COI)	% CV	Mean (COI)	SD (COI)	% CV
Human serum, COI < 7.0	0.42	0.04	9.5	1.57	0.04	2.6
Human serum, COI 7.0 - ≤ 30	0.40	0.02	5.0	4.85	0.10	2.1
Human serum, COI > 30	1.31	0.10	7.6	1321	12.8	1.0

Intra-Assay Precision Without Confirmatory Test Pretreatment

Sample	Mean (COI)	SD (COI)	% CV
Human serum, COI < 7.0	1.65	0.04	2.4
Human serum, COI 7.0 - ≤ 30	11.3	0.11	1.0
Human serum, COI > 30	669	17.7	2.6

For the pretreated samples, coefficients of variation (CV) for the confirmatory samples ranged from 5.0 to 9.5%; CVs for the control samples ranged from 1.0 to 2.6%. The samples without the pretreatment procedure had CVs ranging from 1.0 to 2.6%.

10. Summary of Clinical Studies

10.1. Expected Results

Of 1445 prospective subjects participating in the Elecsys HBsAg clinical study, 41.5% (n = 600) were first time blood donors, asymptomatic for viral hepatitis. All of these subjects were enrolled in Sacramento, CA. The group was Caucasian (61%), African American (10%), Hispanic (2%), Asian (1%), and 26% electing not to provide this information. The group was 58% male and 42% female ranging in age from 17 to 73

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years. There were no confirmed positive results for HBsAg by either the reference or the Elecsys test system among these subjects.

The table below summarizes the Elecsys HBsAg negative and confirmed positive results by age range and gender.

		Elecsys HBsAg Immunoassay Test System				
Age	Gender	Pos	Percent	Neg	Percent	Total
< 10	Male	0	NA	0	NA	0
	Female	0	NA	0	NA	0
10 – 19	Male	0	NA	177	100	177
	Female	0	NA	115	100	115
20 – 29	Male	0	NA	71	100	71
	Female	0	NA	42	100	42
30 – 39	Male	0	NA	45	100	45
	Female	0	NA	46	100	46
40 – 49	Male	0	NA	35	100	35
	Female	0	NA	32	100	32
50 – 59	Male	0	NA	16	100	16
	Female	0	NA	13	100	13
60 – 69	Male	0	NA	2	100	2
	Female	0	NA	4	100	4
70 – 79	Male	0	NA	1	100	1
	Female	0	NA	1	100	1
80 – 89	Male	0	NA	0	NA	0
	Female	0	NA	0	NA	0
90 – 99	Male	0	NA	0	NA	0
	Female	0	NA	0	NA	0
Unknown	Male	0	NA	0	NA	0
	Female	0	NA	0	NA	0
Totals	Male	0	NA	347	100	347
	Female	0	NA	253	100	253
	All	0	NA	600	100	600

The 845 remaining subjects were enrolled from populations considered at risk for viral hepatitis due to lifestyle or behavior. Of these, 448 were outpatients of a health screening clinic, 299 were hospitalized patients and 98 were IV drug users. All 98 IV drug users were enrolled in Baltimore, MD. Of the hospitalized and health screening clinic patients, 444 of the subjects were enrolled in Memphis, TN and 303 in Miami, FL. This collective group was African American (26%), Caucasian (19%), Hispanic (5%), Asian (<1%) or other (<1%) with 49% electing not to provide this information. The group was 49% male and 51% female ranging in age from 8 to 94 years. Six (6) of these subjects were confirmed positive by the both the reference and the Elecsys assay test systems. One specimen was confirmed positive by Elecsys but was not repeat reactive by the reference assay. A follow-up specimen taken 28 days later from the same subject was confirmed positive by both assays showing that the first Elecsys result was correct.

The table below summarizes the Elecsys HBsAg negative and confirmed positive results by age range and gender.

Elecsys HBsAg Immunoassay Test System						
Age	Gender	Pos	Percent	Neg	Percent	Total
< 10	Male	0	NA	1	100	1
	Female	0	NA	0	NA	0
10 – 19	Male	0	NA	7	100	7
	Female	0	NA	10	100	10
20 – 29	Male	1	0.7	135	99.3	136
	Female	3	2.5	117	97.5	120
30 – 39	Male	0	NA	60	100	60
	Female	2	3.1	62	96.9	64
40 – 49	Male	0	NA	56	100	56
	Female	0	NA	65	100	65
50 – 59	Male	0	NA	53	100	53
	Female	0	NA	44	100	44
60 – 69	Male	0	NA	38	100	38
	Female	1	1.9	53	98.1	54
70 – 79	Male	0	NA	33	100	33
	Female	0	NA	46	100	46
80 – 89	Male	0	NA	12	100	12
	Female	0	NA	19	100	19
90 – 99	Male	0	NA	1	100	1
	Female	0	NA	3	100	3
Unknown	Male	0	NA	14	100	14
	Female	0	NA	8	100	8
Totals	Not Given	0	NA	1	100	1
	Male	1	0.2	410	99.8	411
	Female	6	1.4	427	98.6	433
	All	7	0.8	838	99.2	845

10.2. Clinical Performance

A multi-center prospective study was conducted to characterize the performance of the Elecsys HBsAg Immunoassay test system with individuals from defined populations. All subjects were tested using FDA-approved/cleared reference methods in strict accordance with the manufacturer's package insert instructions. The collection sites for the specimens were located in Sacramento, CA (41.5%), Baltimore, MD (6.8%), Memphis, TN (30.7%) and Miami, FL (21.0%).

Of the 1445 prospective subjects participating in the Elecsys HBsAg clinical study, 41.5% (n=600) were first time blood donors, asymptomatic for viral hepatitis and 845 subjects were at risk of HBV infection due to lifestyle or behavior. Of the 845 at risk subjects, 53.0% (n=448) were outpatients of a health screening clinic, 35.4% (n=299) were hospitalized patients and 11.6%(n=98) were IV drugs users.

The first time blood donors were Caucasian (61%), African American (10%), Hispanic (2%), Asian (1%) with 26% electing not to provide this information. The group was 58% male and 42% female ranging in age from 17 to 73 years. The at risk subjects were African American (26%), Caucasian (19%), Hispanic (5%), Asian (<1%) or other (<1%) with 49% electing not to provide this information. This group was 49% male and 51% female ranging in age from 8 to 94 years.

The performance of the Elecsys HBsAg immunoassay test system was analyzed relative to the reference HBsAg reported results for all 1445 specimens. Complete testing using FDA approved methods for all 6 HBV serological markers including HBsAg, HBeAg, anti-HBc, anti-HBc IgM, anti-HBe and anti-HBs, thus allowing cross-sectional serological classifications of HBV status, was available for 382 of the subjects.

HBV classifications were performed based on the constellation of test results from FDA-approved methodologies for various markers of HBV. Elecsys test results were not considered in these classifications. Presented below are the interpretations of HBV classification made for each of the serological profiles observed.

HBV Classification	HBsAg	HBeAg	anti-HBc IgM	anti-HBc	anti-HBe	anti-HBs
Acute	pos	+ or -	-	-	-	-
Acute	pos	+ or -	pos	pos	+ or -	-
Chronic*	pos > 6mo					
Chronic	pos	+ or -	-	pos	+ or -	+ or -
Early Recovery	-	-	pos	pos	+ or -	+ or -
Recovery	-	-	-	pos	pos	+ or -
Recovered	-	-	-	pos	-	+ or -
Vaccinated	-	-	-	-	-	pos
not previously infected	-	-	-	-	-	-
Uninterpretable	pos	-	pos	pos	pos	pos
Uninterpretable	-	pos	-	-	-	-
Uninterpretable	-	pos	-	-	-	pos
Uninterpretable	-	pos	-	pos	-	pos
Uninterpretable	-	-	-	-	pos	pos
Uninterpretable	-	-	-	-	-	equiv

* Subjects known, by testing, to have HBsAg persisting for greater than 6 months.

The following table compares the Elecsys HBsAg results with the reference results for the prospective studies with first time blood donors by HBV classification.

HBV Classification	Final HBsAg Result – Reference Test System	
	Elecsys HBsAg Result	Total
Acute	0	0
Chronic	0	0
Early Recovery	1	1
Recovery	2	2
Recovered	1	1
Uninterpretable	1	1
HBV Vaccine Response	86	86
Not Previously Infected	31	31
Incomplete Testing	478	478
Total	600	600

The table below compares the Elecsys HBsAg results with the reference results for the prospective studies with subjects at risk for HBV infection due to lifestyle or behavior by HBV classification.

HBV Classification	Final HBsAg Result – Reference Test System				
	Elecsys HBsAg Result		Elecsys HBsAg Result		Total
Acute	0	0	0	3	3
Chronic	0	0	0	2	2
Early Recovery	4	0	0	0	4
Recovery	36	0	0	0	36
Recovered	31	0	0	0	31
Uninterpretable	8	0	0	0	8
HBV Vaccine Response	140	0	0	0	140
Not Previously Infected	35	1[a]	0	0	36
Incomplete Testing	584	0	0	1	585
Total	838	1	0	6	845

[a] This specimen was tested using the Roche Molecular Systems HBV Monitor Test and yielded a count of >9600 copies of HBV DNA/mL. A follow-up sample from the same patient taken 28 days after the first sample was confirmed positive on both the reference and Elecsys HBsAg immunoassay test systems.

The table below summarizes the percent agreement between the Elecsys HBsAg Immunoassay Test System and the HBsAg reference assay test system with first time blood donors by specimen classification.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	NA	NA	NA	NA
Chronic	NA	NA	NA	NA
Early Recovery	NA	NA	100 (1/1)	2.5 to 100
Recovery	NA	NA	100 (2/2)	15.9 to 100
Recovered	NA	NA	100 (1/1)	2.5 to 100
Uninterpretable	NA	NA	100 (1/1)	2.5 to 100
HBV Vaccine Response	NA	NA	100 (86/86)	95.8 to 100
Not Previously Infected	NA	NA	100 (31/31)	88.8 to 100
Incomplete Testing	NA	NA	100 (478/478)	99.2 to 100
Overall	NA	NA	100 (600/600)	99.4 to 100

The table below summarizes the percent agreement between the Elecsys HBsAg Immunoassay Test System and the HBsAg reference assay test system with subjects at risk for HBV infection due to lifestyle or behavior by specimen classification. The table also provides the upper and lower 95% Exact Confidence Intervals.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	100 (3/3)	29.5 to 100	NA	NA
Chronic	100 (2/2)	15.9 to 100	NA	NA
Early Recovery	NA	NA	100 (4/4)	40.0 to 100
Recovery	NA	NA	100 (36/36)	90.3 to 100
Recovered	NA	NA	100 (31/31)	88.8 to 100
Uninterpretable	NA	NA	100 (8/8)	63.2 to 100
HBV Vaccine Response	NA	NA	100 (140/140)	97.4 to 100
Not Previously Infected	NA	NA	97.2 (35/36)	85.5 to 100
Incomplete Testing	100 (1/1)	2.5 to 100	100 (584/584)	99.3 to 100
Overall	100 (6/6)	54.1 to 100	99.9 (618/619)	99.5 to 100

The performance of the Elecsys HBsAg Immunoassay test system was studied with archived specimens representing various discrete stages of HBV infection or recovery. The table below compares the Elecsys HBsAg immunoassay test system results with the HBsAg reference assay test system results by specimen classification.

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HBV Classification	Final HBsAg Result Reference Test System				
	Elecsys HBsAg Result		Elecsys HBsAg Result		Total
Acute	0	0	0	151	151
Chronic	0	0	0	111	111
Chronic – HBsAg >6 mo.[a]	0	0	0	74	74
Early Recovery	4	1[b]	0	0	5
Recovery	35	0	0	0	35
Recovered	24	0	0	0	24
Uninterpretable	4	0	0	1	5
HBV Vaccine Response	6	0	0	0	6
Not Previously Infected	9	0	0	0	9
Total	82	1	0	337	420

[a] Subjects known, by testing, to have HBsAg persisting for greater than 6 months.

[b] This specimen by the reference method was repeatedly within 10% of cut-off and showed 100% neutralization but was classified as negative in accordance with reference test's approved package insert instructions since the initial test was below cut-off at 0.94 COI.

The following table summarizes the percent agreement between the Elecsys HBsAg Immunoassay Test System and the HBsAg reference assay test system by specimen classification, and provides the upper and lower 95% Exact Confidence Intervals.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	100 (151/151)	97.6 to 100	NA	NA
Chronic	100 (111/111)	96.7 to 100	NA	NA
Chronic – HBsAg >6 mo	100 (74/74)	95.1 to 100	NA	NA
Early Recovery	NA	NA	80.0 (4/5)	28.6 to 99.5
Recovery	NA	NA	100 (35/35)	90.0 to 100
Recovered	NA	NA	100 (24/24)	85.8 to 100
Uninterpretable	100 (1/1)	2.5 to 100.0	100 (4/4)	40.0 to 100
HBV Vaccine Response	NA	NA	100 (6/6)	54.3 to 100
Not Previously Infected	NA	NA	100 (9/9)	66.5 to 100
Overall	100 (337/337)	98.9 to 100	98.8 (82/83)	93.5 to 100

10.3. Clinical Performance in Pregnant Women

A total of 81 pregnant women were reported from among all subjects in the Elecsys 2010 HBsAg clinical study. All were considered to be at low risk for HBV infection. The table below summarizes the Elecsys 2010 HBsAg final result in comparison to the reference method by age and ethnic group. Information on trimester stage was not available.

			Reference HBsAg Assay Final Result		Elecsys 2010 HBsAg Final Result	
Ethnicity	**Age**	**N**	**Positive**	**Negative**	**Positive**	**Negative**
African-American	10 - 19	5	0	5	0	5
	20 - 29	8	1	7	1	7
	30 - 39	2	0	2	0	2
	40 - 49	0	0	0	0	0
Caucasian	10 - 19	1	0	1	0	1
	20 - 29	7	0	7	0	7
	30 - 39	8	0	8	0	8
	40 - 49	1	0	1	0	1
Not Provided	10 - 19	3	0	3	0	3
	20 - 29	29	1	28	1	28
	30 - 39	15	1	14	1	14
	40 - 49	1	0	1	0	1
	not given	1	0	1	0	1
Overall		81	3 (3.7%)	78 (96.3%)	3 (3.7%)	78 (96.3%)

The table below summarizes the percent agreement between the Elecsys HBsAg Immunoassay Test System and the HBsAg reference assay test system with pregnant women. The table also provides the upper and lower 95% Exact Confidence Intervals.

Subjects	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Pregnant Women	100 (3/3)	29.5 to 100	100 (78/78)	95.4 to 100

10.4. Elecsys HBsAg Confirmatory Test

The Elecsys HBsAg Confirmatory Test was evaluated with all specimens throughout the Elecsys HBsAg clinical study that had been confirmed positive by the FDA-licensed reference HBsAg confirmatory assay. The table below compares the Elecsys HBsAg Confirmatory Test results with the reference HBsAg confirmed positive result.

Sample Sources	N	Reference HBsAg Reactive Specimens Confirmed Positive by Neutralization	Elecsys HBsAg Confirmatory Test Confirmed Positive by Neutralization
First time blood donors	0	NA	NA
Subjects at risk for HBV infection due to lifestyle or behavior	6	6	6
Serologically classified acute HBV infection (archived)	151	151	151
Serologically classified chronic HBV infection (archived)	111	111	111
Chronic HBV infection, HBsAg for > 6months (archived)	74	74	74
Pregnant women	3	3	3
Total	345	345	345 (100%)

11. Conclusions Drawn from PMA Studies

In multi-centered clinical trials in the United States, the Elecsys HBsAg Immunoassay and Elecsys HBsAg Confirmatory Test were shown to exhibit clinical sensitivity and specificity that correlate well to other commercially available similar licensed devices.

The clinical evaluations provide valid scientific evidence of the clinical and diagnostic use of the automated Elecsys HBsAg Immunoassay for the qualitative determination of HBsAg in human serum and plasma (sodium heparin, EDTA-K3 and sodium citrate). The results from these studies also support the clinical and diagnostic performance of the Elecsys HBsAg Confirmatory test (a neutralization test), and the Elecsys HBsAg PreciControl reagents.

The PMA studies provide reasonable assurance that the Elecsys HBsAg Immunoassay can safely and effectively be used to test individuals at various risk for HBV infection and can be used as an aid in the diagnosis of patients with acute or chronic HBV infection. These studies establish the use of the assay to screen for hepatitis B infection in pregnant women to identify neonates at high risk of acquiring HBV during the perinatal period (see caution in the Risk/Benefit section below).

The studies support the use of Elecsys HBsAg Confirmatory Test as an immunoassay for the *in vitro* confirmation of the presence of HBsAg in human serum and plasma (sodium heparin, EDTA-K3, sodium citrate) samples found repeatedly reactive when tested with Elecsys HBsAg Immunoassay.

12. Safety and Benefit/Risk Analysis

As a diagnostic test, the HBsAg assay involves removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is removed.

The benefits to HBV-infected individuals tested by these devices outweigh any potential adverse event or risk to the patient or user due to device malfunction or operator error. The

use of the Elecsys HBsAg Confirmatory test adds a further safety measure for the accurate reporting of confirmed positive test results.

The potential risks seen for *in vitro* diagnostic tests are not unusual in the laboratory setting, and appropriate warnings for these risks are contained in the labeling and package insert instructions for these devices. Standard good laboratory practices are considered sufficient to minimize the risks to the end user.

The clinical studies minimally establish the use of the assay to screen pregnant women to identify neonates at high risk of acquiring HBV during the perinatal period. Users may wish to establish their own specificity for prenatal screening.

13. CDRH Decision on application:

FDA issued an approval order on June 1, 2001.

The applicant's manufacturing facility was inspected on _____ and found to be in compliance with the devices Good Manufacturing Practice regulation.

14. Approval Specifications:

Directions for Use: See labeling

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

Postapproval Requirements and Restrictions: See approval order.